

14. (CANCELED)

C2 15. (AMENDED) A pharmaceutical composition comprising [the secretory IgA] a secretory Ig produced by the method of claim 1 [14] and a pharmaceutically acceptable carrier.

Ende A. 12-14-28
(NEW) A method of producing secretory Ig (sIg) molecules comprising transfecting a non-plant cell with a polynucleotide encoding an Ig and with a polynucleotide encoding secretory component (SC) to form an SC transfected Ig producing cell, and culturing the SC transfected Ig producing cell so as to produce secretory Ig molecules.

15 28 14
(NEW) The method of claim 16, wherein the Ig molecule is an IgA.

16 28 14
(NEW) The method of claim 16, wherein the Ig molecule is a domain-modified IgA.

E3 C3 17 28 14 non-plant
(NEW) The method of claim 16, wherein the cell is a mammalian, avian, insect, bacterial or yeast cell.

18 17 31 14
(NEW) The method of claim 19, wherein the mammalian cell is a human, rabbit, murine, rat or bovine cell.

19 28 14 non-plant
(NEW) The method of claim 16, wherein the cell is a myeloma cell, CHO cell, L cell, COS cell, fibroblast, MDCK cell, HT29 cell or a T84 cell.

REMARKS

I. Introduction

In response to the Office Action dated May 24, 2000, claim 14 has been cancelled, claims 1 and 15 have been amended, and new claims 16-21 have been added. Claims 1-13 and 15-21 remain in the application. Reconsideration of the application, as amended, is requested.

II. Claim Amendments

Applicants' attorney has made amendments to the claims as indicated above. Claim 1 was amended to explicitly exclude plant cells. Claim 15 was amended to remove the dependency from canceled claim 14. New claim 16 is supported by pending claims 1 and 8; new claims 17-21 are supported by pending claims 12, 13, and 9-11, respectively. These amendments to the claims introduce no new matter, and their entry is respectfully requested.

III. Examiner Interview

Reference is hereby made to telephone interviews on May 18 & 19, and August 23, 2000, between Applicants' undersigned attorney and Examiner Zeman, in connection with the present patent application. In these interviews, the Hein et al. reference was discussed, and Examiner Zeman indicated that amendment of the claims to exclude plant cells would put the claims in condition for allowance.

IV. Prior Art Rejections

At pages 2-4 of the Office Action, claim 14 was rejected under 35 U.S.C. § 102 as allegedly unpatentable over Weltzin (U.S. Patent No. 5,534,411) or Hein (U.S. Patent No. 5,959,177). This rejection is now moot in view of the cancellation of claim 14. Applicants do not concede that the product of the claimed process cannot be distinguished from secretory immunoglobulins produced by other processes, and reserve the right to pursue this claim in a separate application.

At pages 4-6 of the Office Action, claims 1-15 were rejected under 35 U.S.C. § 102 as allegedly unpatentable over Weltzin (U.S. Patent No. 5,534,411) in view of Hein (U.S. Patent No. 5,959,177). In view of the amendment to claim 1 and the arguments presented below, Applicants respectfully request withdrawal of this rejection.

The claimed invention is directed to a method of producing secretory Ig (sIg) molecules comprising transfecting a non-plant cell producing an Ig with a polynucleotide encoding secretory component (SC) to form an SC transfected Ig producing cell, and culturing the SC transfected Ig producing cell so as to produce secretory Ig molecules. This claim is supported by working examples described at pages 13-19 of the specification. These examples include details regarding: cloning of the human secretory component (SC; Example 1, p. 13); expression of cloned SC in cells

secreting IgA (Example 2, p. 14); analysis of culture supernatants to confirm production of secretory Ig (Example 3, p. 14); pulse-chase experiments to analyze assembly of SC and IgA, confirming that SC was covalently linked to Ig intracellularly (Example 4, p. 14-16); and confirmation of *in vivo* stability of the secretory Ig so produced (Example 5, p. 16-19).

Weltzin discloses a monoclonal IgA antibody (HNK20) specific for respiratory syncytial virus produced by a hybridoma. Throughout the summary, detailed description, examples and claims of the Weltzin patent, the HNK20 antibodies are taught in a preferred form, "substantially pure" and "free from other immunological material" (col. 3, l. 33-35). The one exception appears in the paragraph at column 11, lines 39-59, which teaches that the disclosed HNK20 IgA antibodies "can be bound to secretory component to yield complexes with increased resistance to digestion by proteolytic enzymes." The text then goes on to list three alternative methods for achieving SC combined with polymeric IgA. One of these three alternative suggestions includes transfecting a hybridoma that produces HNK20 with an expression vector containing the cDNA for secretory component. As established in the Amendment and Declaration by Dr. Sherie L. Morrison submitted by Applicants on March 8, 2000, this prophetic statement is not supported by working examples, nor would those skilled in the art have had a reasonable expectation of success in attempting the suggested method in the absence of actual data supporting the suggestion.

Hein discloses and claims a method of producing sIgA in plant cells through successive sexual crossing of three separate transformants: one genetically modified to produce a mammalian Ig, one to produce J chain, and one to produce SC. Hein discusses the advantages of using plant cells over mammalian and other cell systems (column 1, lines 25-48), and the remote probability of successfully introducing more than one gene into a single plant cell prior to the method of crossing multiple transformants disclosed therein (column 2, lines 9-16). Hein teaches that the successive sexual crossing of multiple transformants is necessary to achieve a single plant cell capable of producing a secretory IgA-G. The disclosure of Hein therefore teaches away from both the use of non-plant cells and the introduction of multiple genes into a single cell.

At pages 5-6 of the Office Action, it is argued that the disclosure of Hein, together with Weltzin, would create a reasonable expectation of success in producing a sIg molecule in a single cell by transfecting an Ig-producing cell with a vector encoding SC. While Applicants disagree with this assertion, the amendment of the claims to exclude plant cells renders this rejection moot.

Moreover, those of skill in the art would not expect the production of sIgA-G in plant cells through successive sexual crosses to be predictive of success with transfecting a non-plant Ig-producing cell with a vector encoding SC to achieve production of sIg in a non-plant cell. As set forth in the Amendment of March 8, 2000, and in Dr. Morrison's Declaration submitted therewith, those skilled in the art had several reasons to doubt the capability of a single cell to produce a complete secretory immunoglobulin molecule, even though the work of Ma et al. using plant cells was already known (Ma et al., 1995, Science 268:716-719; attached to the Morrison Declaration as Exhibit A; provided previously as Exhibit 8 of PTO Form 1449; and cited at page 3 of the specification; same group as Hein et al. of the cited reference). In addition to the presumptions held by those in the art that production of sIgA in mammalian cells required multiple cells, the skilled artisan would also be deterred by the inherent differences between plant and non-plant cells, as discussed in the specification at page 3, lines 4-9. These differences include the attachment of different sugar residues resulting in glycosylation properties that would be expected to affect the functional properties of the resulting molecule.

As evidenced by the comments made in an electronic mail communication received by Dr. Morrison on September 29, 1998, from Dr. Blaise Corthésy of the Division of Immunology and Allergology of the State Hospital in Lausanne, Switzerland (Exhibit 3 of Morrison Declaration), those skilled in the art did not expect, prior to the publication of Dr. Morrison's work, that individual non-plant cells could be made to perform the "whole job of assembling a whole secretory IgA molecule", and that this method would provide "an attractive alternative to the in vitro reconstitution using purified secretory component and dimeric IgA." It was the disclosure of Applicants' data that enabled those skilled in the art to successfully produce sIgA in a single non-plant cell. In view of the doubts held by those skilled in the art and the successful teaching disclosed in Applicants' specification, independent claim 1 is patentable over the cited references, individually and in combination.

V. Dependent Claims

Dependent claims 2-13 and 15 incorporate the limitations of related independent claim 1, and are therefore patentable on this basis. In addition, these claims recite novel elements even more

remote from the cited references. Accordingly, the Applicants respectfully request that these claims be allowed as well.

VI. New Claims

New Claims 16-21 are presented for the first time in this Amendment. For the reasons described above, new claims 16-21 are patentable over the prior art of record, and the Applicants respectfully request the allowance of these claims as well.

VII. Conclusion

In view of the above, it is submitted that this application is now in good order for allowance and such allowance is respectfully solicited. Should the Examiner believe minor matters still remain that can be resolved in a telephone interview, the Examiner is urged to call Applicants' undersigned attorney.

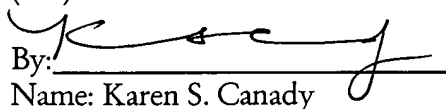
Respectfully submitted,

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By their attorneys,

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